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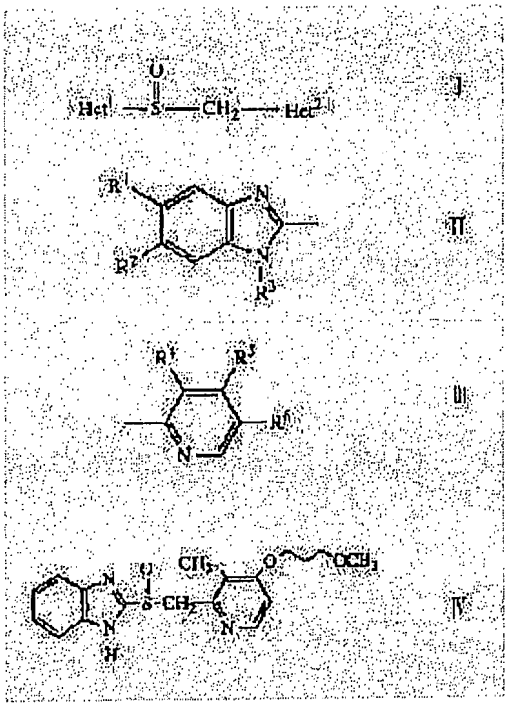
(54) **STABILIZED COMPOSITION COMPRISING BENZIMIDAZOLE-BASED COMPOUND**



(57)Abstract:
PROBLEM TO BE SOLVED: To obtain the subject composition capable of further stabilizing a solid drug preparation for internal use comprising a benzimidazole-based compound by formulating the benzimidazole-based compound and a specific substance.
SOLUTION: This composition is obtained by formulating (A) a benzimidazole- based compound of formula I (Het1 is of formula II; Het2 is of formula III; R1 and R2 are each H, methoxy or difluoromethoxy; R3 is H or sodium, R4 to R6 are each H, methyl, methoxy, methoxypropoxy or trifluoroethoxy) (e.g. rabeprazole of formula IV) with (B) a substance selected from e.g. a sodium carbonate, sodium hydroxide, potassium hydroxide, crospovidone, at preferably 0.01-20 pts.wt per pt.wt. of the ingredient A. It is also possible to make a drug preparation by coating a core composed of the above composition with an intermediate film, enteric film or moistureproof film.

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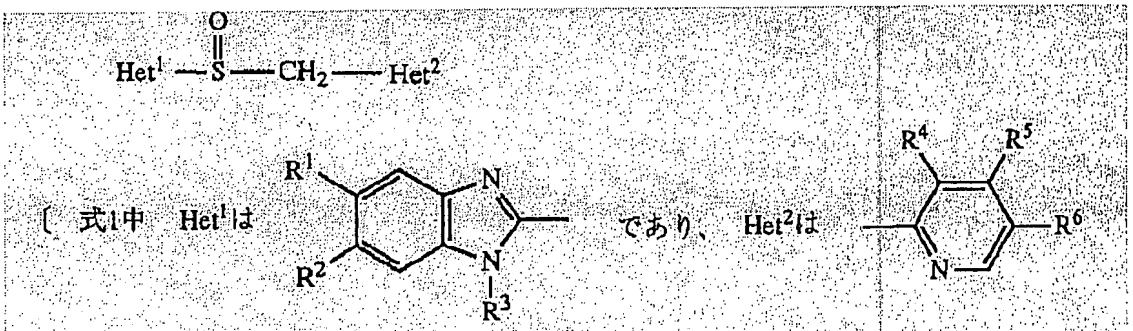
TECHNICAL FIELD

[Field of the Invention] This invention relates to the solid preparations for oral administration containing a benzimidazole system compound or its alkali-metal salt.

[Claim(s)]

[Claim 1] The constituent which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown with the following structure expression (formula 1), or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone.

[Formula 1]



(式1)

[Claim 2] The constituent according to claim 1 whose benzimidazole system compound is rabeprazole, omeprazole, punt PURAZORU, lansoprazole, or its alkali-metal salt.

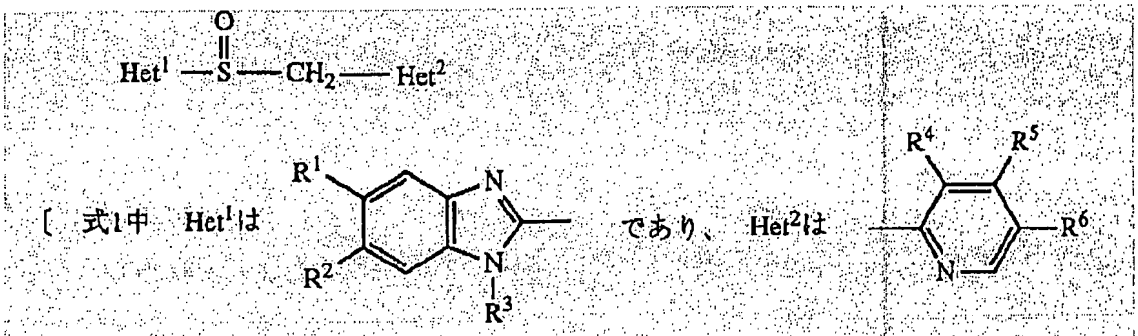
[Claim 3] The constituent according to claim 1 whose rate of a compounding ratio with a benzimidazole system compound or its alkali-metal salt, a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide,

Aminoalkylmetaacrylatecopolymer E and an arginine aspartic-acid salt, hydroxypropylcellulose, and/or cross povidone is 0.01 - 20 weight section in a total amount to the benzimidazole system compound 1 weight section.
[Claim 4] Pharmaceutical preparation which covered the enteric sex skin film in the nucleus which comes to blend one or more sorts of matter chosen from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone with the benzimidazole system compound shown by the formula 1, or its alkali-metal salt.
[Claim 5] Pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone with the benzimidazole system compound shown by the formula 1, or its alkali-metal salt, and covered the enteric sex skin film further.
[Claim 6] Pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone with the benzimidazole system compound shown by the formula 1, or its alkali-metal salt, covered the enteric sex skin film further, and then covered the moisture-proof sex skin film.
[Claim 7] The constituent which comes to blend a sodium hydroxide, a potassium hydroxide, and/or a sodium carbonate with rabeprazole or its alkali-metal salt [claim 8] The constituent which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with rabeprazole or its alkali-metal salt [claim 9] Pharmaceutical preparation which covered the enteric sex skin film in the nucleus which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with rabeprazole or its alkali-metal salt [claim 10] Pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with rabeprazole or its alkali-metal salt, and covered the enteric sex skin film further [claim 11] Pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with rabeprazole or its alkali-metal salt, covered the enteric sex skin film further, and then covered the moisture-proof sex skin film.
[Claim 12] The stable constituent or pharmaceutical preparation [claim 13] to which it makes it come to blend an anti-oxidant with the constituent according to claim 8 which blended cross povidone, or a nucleus according to claim 9 to 11 Pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the enteric sex skin film in gastric acid in the nucleus which comes to blend an unstable drug chemically, and covered the moisture-proof sex skin film further.
[Claim 14] Pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the middle coat in gastric acid in the nucleus which comes to blend an unstable drug chemically, covered the enteric sex skin film further, and

then covered the moisture-proof sex skin film.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the solid preparations for oral administration containing a benzimidazole system compound or its alkali-metal salt.
[0002]
[Description of the Prior Art] A benzimidazole system compound or its alkali-metal salt has the so-called strong inhibitory action of a proton pump, and is widely used as therapy agents, such as a gastric ulcer and a duodenal ulcer, by controlling gastric-acid secretion. On the other hand, various devices are made [in / since it is chemical very unstable / in a benzimidazole system compound / pharmaceutical-preparation-izing]. For example, the process of the stable physic constituent characterized by to blend the basic mineral salt of magnesium and/or calcium at JP,62-277322,A at a benzimidazole system compound is indicated, and the oral physic pharmaceutical preparation which blends an alkali compound with the nucleus part which contains a benzimidazole system compound in JP,62-258320,A, covers with a film formation compound water-soluble with the excipient of the tablet quickly disassembled with water solubility thru/or water or a polymer etc., and is further covered with the enteric sex skin film is indicated.
[0003]
[Problem(s) to be Solved by the Invention] However, also by the above-mentioned technique, the stability in pharmaceutical preparation is not enough and the further improvement is called for. Namely, this invention aims at much more stabilization of the solid preparations for oral administration containing a benzimidazole system compound.
[0004]
[Means for Solving the Problem] This invention is a constituent which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown with the structure expression (formula 1) shown below, or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone.
[Formula 2]



〔式1中　Het^1は　　であり、　Het^2は　　

であり、R^1およびR^2は同じかまたは異なっていて、水素、メトキシ及びジフルオロメトキシから選択され、R^3は水素及びナトリウムから選択され、R^4、R^5およびR^6は同じかまたは異なっていて、水素、メチル、メトキシ、メトキシプロポキシ及びトリフルオロエトキシから選択される。〕

（式1）

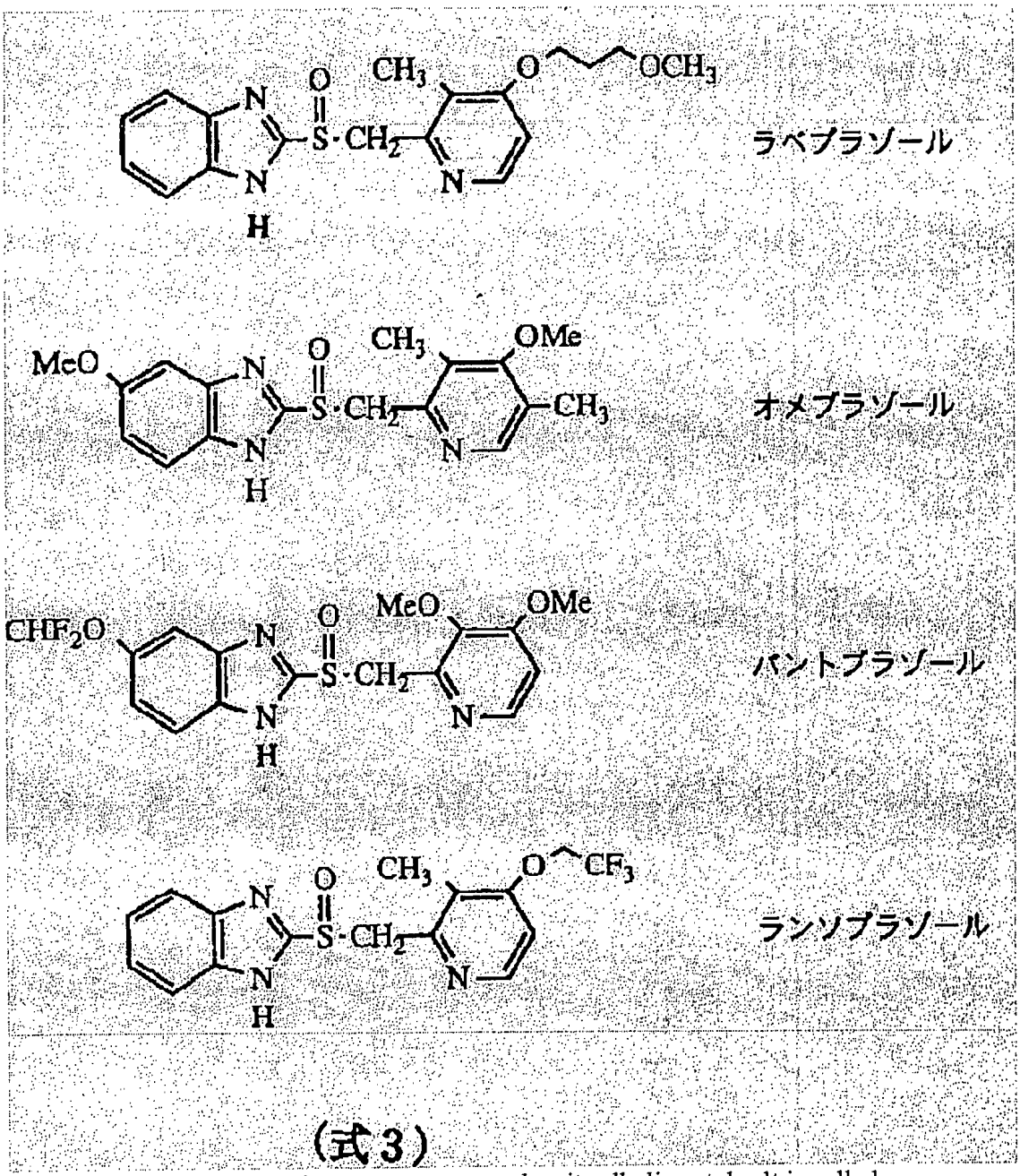
[0005] Furthermore, this invention is the pharmaceutical preparation which covered the enteric sex skin film in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1, or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone. Moreover, this invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1, or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, and covered the enteric sex skin film further. This invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, covered the enteric sex skin film further in the benzimidazole system compound shown by the formula 1, or its alkali-metal salt, and then covered the moisture-proof sex skin film in it again.

[0006] The moisture-proof sex skin film is useful also to the drug with which it does not remain in a benzimidazole system compound, decomposition is promoted under moisture existence, and promotion of decomposition is accepted also at the time of contact to gastric acid. That is, this invention is the pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the enteric sex skin film in gastric acid in the nucleus which comes to blend an unstable drug chemically, and covered the moisture-proof sex skin film further. Moreover, this invention is the pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the middle coat in gastric acid in the nucleus which comes to blend an unstable drug chemically, covered the enteric sex skin film further, and then covered the moisture-proof sex skin film.

[0007] As a desirable example of the benzimidazole system compound in this invention,

or its alkali-metal salt, rabeprazole, omeprazole, punt PURAZORU, lansoprazole or its sodium salt, potassium salt, etc. can be mentioned. The structure expression of each compound is shown in a formula 3.

[Formula 3]



(式3)

Hereafter, a benzimidazole system compound or its alkali-metal salt is called a benzimidazole system compound.

[0008] The benzimidazole system compound in this invention can be manufactured by the well-known approach. For example, it can manufacture by the approach indicated by JP,52-62275,A, JP,54-141783,A, JP,1-6270,A, etc.

[0009] The sodium carbonate in this invention, potassium carbonate, a sodium hydroxide,

a potassium hydroxide, and hydroxypropylcellulose are Japanese pharmacopoeia adoption articles, and can obtain a commercial thing easily. Adoption of the aminoalkylmetaacrylatecopolymer E is carried out to Japanese Pharmaceutical Codex, and it is easily available. Moreover, although cross povidone is matter by which adoption is carried out to excipient specification and is easily available in the commercial item of various grade with which particle size differs, particle size can be adjusted using grinding equipments, such as a hammer mill, if needed. To the benzimidazole system compound 1 weight section, the rate of a compounding ratio with one or more sorts of matter chosen from the benzimidazole system compound in this invention, a sodium carbonate and potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone is 0.01 - 20 weight section in a total amount, and is 0.01 - 10 weight ****** preferably. In this invention, a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone can also be used independently, and two or more sorts can also be used combining these. It is [among these] effective for a benzimidazole system compound to blend a sodium hydroxide, a potassium hydroxide, and/or a sodium carbonate, and it is still more effective if 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate are blended with a benzimidazole system compound. In the combination of this matter, although the rate of a compounding ratio is 0.01 - 20 weight section to the benzimidazole system compound 1 weight section, cross povidone is [0.5 - 5 weight section, a sodium hydroxide, a potassium hydroxide, and/or a sodium carbonate] 0.01 - 2 weight sections desirably.

[0010] a benzimidazole system compound -- warming -- especially at the time of the decomposition under - humidification preservation conditions, the tinctorial change of a color is accepted greatly. The constituent and/or pharmaceutical preparation which blended the above-mentioned various additives in this invention have the very remarkable effectiveness of controlling not only the improvement in content stability but a tinctorial change.

[0011] In order to manufacture pharmaceutical preparation using the constituent which comes to blend one or more sorts of matter chosen from the benzimidazole system compound concerning this invention, a sodium carbonate and potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, excipients usually used, such as a lactose and a mannitol, can be used. It is desirable to use cross povidone as hydroxypropylcellulose and disintegrator as a binder. Moreover, when the cross povidone generally used as disintegrator pulverizes, it is known that the collapse force as original disintegrator and the swelling force can be decreased. The addition which uses it as a stabilizing agent of a benzimidazole system compound in this invention, and exceeds the addition (usually 10% or less) as usual disintegrator is possible for the small cross povidone of the pulverizing-ized particle size. The pulverizing-ized mean particle diameter of cross povidone has several micrometers - 50 micrometers and 4 micrometers - still more desirable 50 micrometers. Therefore, as for cross povidone, in the constituent or pharmaceutical preparation concerning this invention, it is desirable that mean particle diameter uses several micrometers - 50

micrometers and desirable fines cross povidone with a small particle size of 4 micrometers - 50 micrometers. Of course, fines cross povidone and the usual cross povidone may be used together. Moreover, in cross povidone, although it changes with a manufacture manufacturer or lots, the peroxide of ultralow volume is contained as an impurity in many cases. Since a benzimidazole system compound has the property which is easy to oxidize, it may make an anti-oxidant contain at the time of combination to cross povidone. An anti-oxidant is not necessarily limited to these, although a sodium sulfite, a sodium pyrosulfite, vitamin E, a Rongalite, the thioglycerol, a sodium thiosulfate, an ascorbic-acid salt, acetylcysteine, etc. are mentioned.

[0012] Moreover, this invention is the pharmaceutical preparation which covered the enteric sex skin film in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1 from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone. In this invention, a nucleus means a tablet, a granule, etc. Moreover, as for this invention, the pharmaceutical preparation which covered the enteric sex skin film also contains one or more sorts of matter chosen from a benzimidazole system compound, a sodium carbonate and potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone in regular placing or the nucleus which it comes to coat by using as seed granulation the spherical granulation which consists of purified sucrose, white soft sugar and starch mixture, or crystalline cellulose. The benzimidazole system compound is very unstable in an acid condition, and when a benzimidazole system compound is taken, if it contacts gastric acid in the stomach, it will decompose immediately and it will lose the bioactive. Therefore, in order to prevent the decomposition in the stomach, it is necessary to carry out to the pharmaceutical preparation which does not dissolve within the stomach, i.e., the pharmaceutical preparation which covered the enteric matter in the nucleus containing a benzimidazole system compound.

[0013] Furthermore, this invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1 from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, and covered the enteric sex skin film further. Since the enteric sex skin film is generally the acid, direct contact to a benzimidazole system compound is not desirable. Then, an inactive middle coat can be given in the middle of the nucleus containing a benzimidazole system compound, and the enteric sex skin film. Inactive is matter which does not have a bad influence on the stability of a benzimidazole system compound here. Any of a water soluble polymer, dissolved water in fuel or the water-dispersion matter, and the water-insoluble nature matter are sufficient as an inactive middle coat, and, specifically, it can mention hydroxypropylcellulose, the hydroxypropyl methylcellulose, Aminoalkylmetaacrylatecopolymer E, a lactose, a mannitol, starch, crystalline cellulose, ethyl cellulose, vinyl acetate, etc. In addition, when giving a middle coat by the water-insoluble nature matter as indicated by JP,1-290628,A, the particle of water-insoluble

nature may be mixed in a coat.
[0014] This invention may cover the moisture-proof sex skin film again to the pharmaceutical preparation which covered the above-mentioned enteric sex skin film. The moisture-proof sex skin film is a coat which controls passage of a steam, and, functionally, the coat which captures a steam and controls the inflow of the steam to the interior is mentioned into the coat to which the coat itself controls the permeability of a steam, or a coat. The moisture-proof sex skin film has the function to prevent a crack and deformation of the tablet originating in the swelling at the time of the pulverizing-ized moisture absorption of cross povidone while it defends invasion of the moisture to a benzimidazole system compound and raises stability. The moisture-proof sex skin film is not necessarily limited to these, although the coat which comes to blend one or more sorts of cellulosics, such as a coat which a water-soluble coat or the water-insoluble sex skin film is sufficient as, for example, consists of polyvinyl-acetal diethylamino acetate, HA Sankyo (mixture of polyvinyl-acetal diethylamino acetate, the hydroxypropyl methylcellulose, stearin acid, and a fumaric acid), polyvinyl alcohol, etc., and hydroxypropylcellulose, hydroxypropyl methylcellulose, ethyl cellulose, the glycocalyx coat which uses white soft sugar as a principal component are mentioned.
[0015] The moisture-proof sex skin film is useful also to the pharmaceutical preparation containing the drug which does not remain in a benzimidazole system compound but has the same chemical property. That is, in the pharmaceutical preparation containing the drug with which decomposition is promoted under moisture existence, and promotion of decomposition is accepted also at the time of contact to gastric acid, effectiveness is accepted notably. That is, this invention is the pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the enteric sex skin film in gastric acid in the nucleus which comes to blend an unstable drug chemically, and covered the moisture-proof sex skin film further. Moreover, a middle coat may be covered between the enteric sex skin film and the moisture-proof sex skin film.
[0016] In this invention, when the benzimidazole system compound expressed with a formula 1 is rabeprazole, the especially excellent effectiveness is shown. That is, this invention is a constituent which comes preferably to blend a sodium hydroxide, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt. Moreover, this invention is a constituent which comes preferably to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt. As for cross povidone, it is desirable to use what pulverized mean particle diameter to several micrometers - 50 micrometers as mentioned above. Moreover, an anti-oxidant may be added in order to prevent the effect of the peroxide of the ultralow volume contained in cross povidone as mentioned above. Therefore, an anti-oxidant may be blended into the constituent which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with rabeprazole or its alkali-metal salt.
[0017] This invention is the pharmaceutical preparation which covered the enteric sex skin film preferably again in the nucleus which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt. Furthermore, this invention is the pharmaceutical preparation which covered the middle coat in the nucleus which

comes preferably to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt, and covered the enteric sex skin film further. This invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt, covered the enteric sex skin film further, and then covered the moisture-proof sex skin film preferably again.

[0018] The constituent or pharmaceutical preparation concerning this invention can be manufactured by the approach usually used. That is, for example, one or more sorts of matter chosen as a benzimidazole system compound or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone is blended, an excipient is added, dry type or wet agglomeration is performed, and if needed, disintegrator, such as cross povidone, can be added, and can be tableted and **(ed). Moreover, for example, after preparing the benzimidazole content granulation which blended with high density one or more sorts of matter chosen from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, and the placebo granulation which does not contain a benzimidazole system compound, both granulation may be mixed in a benzimidazole system compound or its alkali-metal salt, and you may add and tablet disintegrator, such as cross povidone, in it if needed. Of course, it is not necessarily limited to these approaches. The hydroxypropylcellulose dissolved in ethanol is added gradually, and is corned, mixing sadium rabeprazole 100g [which is a benzimidazole system compound], 30g [of sodium carbonates], and mannitol 130g, and mixing further as an example, and screening is carried out by 24 mesh sieves after desiccation. Cross povidone 30g and 2g of calcium stearates can be added to this, it can tablet after mixing, and a tablet with one lock of 135mg can be obtained. Fluid bed equipment can be used for this tablet, the ethanol solution of hydroxypropylcellulose can be sprayed, and the enteric coated tablets which sprayed hydroxypropylmethylcellulose phthalate, or the water / ethanol solution of an enteric methacrylic acid copolymer, and gave the middle coat can be manufactured further.

[0019]

[Effect of the Invention] According to this invention, stabilization of a very unstable benzimidazole system compound is possible. The example of effectiveness is shown below.

450mg of additives shown in example sadium rabeprazole of experiment 50mg and the following table was mixed with the mortar. This was put into the transparent carboy, it saved for one week at a cool place, 60 degrees C, and 75% of 40-degree-C relative humidity, and the content was measured with high performance chromatography. The survival rate under the monograph affair when making the content of a cool place preservation article into 100% was shown in Tables 1-3. Moreover, viewing estimated the tinctorial change of a color. In Table 1, the crystalline substance was used for sadium rabeprazole in an amorphous substance, Table 2, and Table 3. In addition, what blended the hydroxypropylcellulose (front Naka L-HPC and display) used as disintegrator besides

an amorphous sadium rabeprazole independent as contrast in Table 1 is used. The sample which blended the polyvinyl pyrrolidone (front Naka PVP and display) used as a binder in Table 3 was used using what blended the aluminum hydroxide (front Naka (OH) aluminum 3 and display) which is the alkaline mineral salt further used as antacid in Table 2.

[0020]

[Table 1]

表2　ラベプラゾールナトリウム(結晶質)の接触試験

		60℃	40℃-75%RH
対照	ラベプラゾールナトリウム(結晶質)	99.8	91.8
	ラベプラゾールナトリウム+L-HPC	62.2	75.0
	ラベプラゾールナトリウム+Al(OH)3	36.9	26.2
本願	ラベプラゾールナトリウム+クロスポビドン	93.3	89.5
	ラベプラゾールナトリウム+Na2CO3	99.1	90.3
	ラベプラゾールナトリウム+Arg・Asp	97.5	90.7

単位：%

表3　ラベプラゾールナトリウム(結晶質)の接触試験

		60℃	40℃-75%RH
対照	ラベプラゾールナトリウム(結晶質)	97.3	86.9
	ラベプラゾールナトリウム+PVP	89.5	67.7
本願	ラベプラゾールナトリウム+ヒドロキシプロピルセルロース	92.0	86.9
	ラベプラゾールナトリウム+Na2CO3	93.0	82.8
	ラベプラゾールナトリウム+NaOH	91.6	98.8
	ラベプラゾールナトリウム+KOH	92.6	96.8
	ラベプラゾールナトリウム+ オイドラギットE	102.4	86.0
	ラベプラゾールナトリウム+K2CO3	104.5	81.3

単位：%

the tinctorial change of the combination sample concerning the invention in this application is all small as compared with contrast -- it cut. Furthermore, the sodium carbonate which starts the invention in this application from the result of the content stability of Tables 1-3 (front Naka Na2CO3 and display), Potassium carbonate (front Naka K2CO3 and display), a sodium hydroxide (front Naka NaOH and display), A potassium hydroxide (front Naka KOH and display), Aminoalkylmetaacrylatecopolymer E (front Naka OIDORAGITTO E (trademark) and display) It is clear cross povidone's [an arginine aspartic-acid salt (front Naka Arg-Asp and display), hydroxypropylcellulose, and] to stabilize a benzimidazole system compound.

[0023] After saving the tablet with which the sodium-carbonate additions obtained in the examples 4-9 shown in the effectiveness following of the sodium carbonate in a tablet differ for one week at 75% of 40-degree-C relative humidity, the sadium rabeprazole content in the tablet measured with the high speed liquid chromatography was shown in Table 4.

[0024]

[Table 4]

表4　湿式造粒法による錠剤処方の安定性評価

処方	実施例4	実施例5	実施例6	実施例7	実施例8	実施例9
(1週間)						
冷所	99.4	99.0	98.7	99.4	99.5	98.9
40°C-75%RH	83.8	85.7	85.1	92.5	92.8	95.5
(1ヶ月)						
冷所	99.7	99.7	99.7	99.7	99.7	99.6
25°C-75%RH	97.8	98.5	98.3	99.2	99.3	99.3

単位：%

[0025] Since the sadium rabeprazole content stability in a tablet improves depending on the addition of a sodium carbonate, the addition effectiveness of the sodium carbonate in this invention is clear.

[0026] After saving the tablet with which the additions of the cross povidone powder obtained in the examples 10-12 shown in the effectiveness following of the cross povidone in a tablet differ for one week at 75% of 40-degree-C relative humidity, the sadium rabeprazole content in the tablet measured with the high speed liquid chromatography was shown in Table 5. Moreover, there were so few tinctorial changes of a tablet that there were many additions of cross povidone powder about change of the color of a tablet.

[0027]

[Table 5]

表5　湿式造粒法によるクロスポビドン添加錠剤の安定性

処方	実施例10	実施例11	実施例12
(1週間)			
冷所	99.7	99.7	99.7
40°C-75%RH	97.8	98.5	98.3
(1ヶ月)			
冷所	99.4	99.0	98.7
40°C-75%RH	83.8	85.7	85.1

単位：%

It is distinct that the stability of a benzimidazole system compound will improve if cross povidone is added.

[0028] After saving respectively the thickness of the tablet which added the cross povidone from which the mean diameter obtained in the examples 16-18 shown in the effectiveness following of the pulverization cross povidone in a tablet differs for one month at a cool place and 75% of 25-degree-C relative humidity, it was measured, and the expansion coefficient to the cool place preservation tablet of 75% preservation tablet of 25-degree-C relative humidity was evaluated. Consequently, the expansion coefficients of the tablet containing cross povidone (51 micrometers of mean diameters, 12 micrometers, and 6 micrometers) were 1.61, 1.48, and 1.43 respectively. In order that the degree of swelling of a tablet may decrease so that it is made fines with small mean

particle diameter, cross povidone's check crack and deformation resulting from expansion of a tablet decrease. Therefore, the pulverization of contribute [to the improvement in stability of the configuration of a tablet] of cross povidone is clear.

[0029] after saving the enteric sex skin film covering tablet obtained in the examples 19-20 shown in the effectiveness following of the moisture-proof sex skin film given to the pharmaceutical preparation which covered the enteric sex skin film, and the tablet which covered both enteric sex skin film and moisture-proof sex skin film for one week at 75% of 25-degree-C relative humidity -- the relative of the sadium rabeprazole in a tablet -- the amount of substance was measured with high performance chromatography. consequently, the relative of an enteric sex skin film covering tablet and the tablet which covered both enteric sex skin film and moisture-proof sex skin film -- the amounts of substance were each, 2.88%, and 2.23%. It is clear pharmaceutical preparation's which covered both enteric sex skin film and moisture-proof sex skin film to have an EQC or the stability beyond it as compared with an enteric sex skin film covering tablet.

[0030] After saving respectively the thickness of the placebo tablet obtained in the examples 21-23 shown below for one week at a cool place and 75% of 40-degree-C relative humidity, it was measured, and the expansion coefficient to the cool place preservation tablet of 75% preservation tablet of 40-degree-C relative humidity was evaluated. Consequently, the expansion coefficients of the tablet which covered the moisture-proof sex skin film which changes from white soft sugar to an enteric sex skin film covering tablet and an enteric sex skin film covering tablet, and the tablet which covered the moisture-proof sex skin film which changes from HA (Sankyo) (mixture of polyvinyl-acetal diethylamino acetate, hydroxy PIROPIRU methyl cellulose, macro gall, and talc) to an enteric sex skin film covering tablet were 1.15, 1.03, and 1.12 respectively. As for the pharmaceutical preparation which covered both enteric sex skin film and moisture-proof sex skin film, it is distinct that the stability of the configuration of a tablet improves as compared with an enteric sex skin film covering tablet since the degree of swelling of the tablet at the time of preservation is small.

[0031] the tablet which added the cross povidone which was obtained in the examples 24-26 shown in the effectiveness following of the anti-oxidant added into the nucleus part containing a benzimidazole system compound, and from which the amount of content peroxides differs -- using -- a high speed liquid chromatography -- the relative of the rabeprazole in a tablet -- the amount of substance was measured. consequently, the early stages of the tablet which added the cross povidone whose peroxide contents are 18 ppm, 190 ppm, and 310 ppm -- a relative -- decomposition of sadium rabeprazole promotes it, so that the amount of substance has many amounts of peroxides which are 0.65% of each, 0.88%, and 1.13%, and are contained in cross povidone -- having -- a relative -- the increment in the amount of substance was accepted.

[0032] Moreover, after the amount of content peroxides could weigh precisely cross povidone 1g which is 201 ppm, could add the sodium sulfite (addition: un-adding, 0.02%, 0.05%, and 0.10% of four levels) and was mixed, the amount of peroxides in mixture was measured according to the method of examining a Japanese pharmacopoeia publication. Consequently, the amounts of peroxides in the constituent whose additions of a sodium sulfite are un-adding, 0.02%, 0.05%, and 0.10% were 201 ppm, 184 ppm, 108 ppm, and 0 ppm respectively, and reduction of the amount of peroxides was accepted, so that the sodium-sulfite addition increased.

[0033] From the above thing, it is distinct by adding an anti-oxidant into the nucleus parts of a benzimidazole system compound and the tablet containing cross povidone that the stability of the benzimidazole system compound in pharmaceutical preparation improves.
[0034]
[Example] Although an example is given to below and this invention is further explained to a detail, this invention is not necessarily limited to these.
[0035] The tablet with one lock of 120mg which adds gradually hydroxypropylcellulose 2.5g dissolved in ethanol, corns and carries out after [desiccation] screening, adds and tablets calcium stearate, and contains 10mg of sadium rabeprazole was obtained having added 10g [of sodium carbonates], and mannitol 100g to example 1 sadium-rabeprazole 10g, and mixing.
[0036] The spray of the solution which dissolved hydroxypropylmethylcellulose phthalate 10g in 2:8 mixed solvents of water ethanol was carried out to the tablet obtained in the example 2 example 1 using fluidized bed granulator, and the enteric coated tablets was manufactured.
[0037] After using fluidized bed granulator for the tablet obtained in the example 3 example 1 and carrying out the spray of the ethanol solution of hydroxypropylcellulose to it, it was operated like the example 2 and the enteric coated tablets was obtained.
[0038] Having added respectively sodium carbonates 0-10g and Mannitols 15-90g to example 4 - 9 sadium-rabeprazole 10g, and mixing, the hydroxypropylcellulose 0.7-2g dissolved in ethanol was added gradually, churning wet agglomeration was carried out, and chief remedy granulation was prepared. Moreover, churning wet agglomeration was performed adding independently hydroxypropylcellulose 2g dissolved in ethanol to mannitol 100g gradually, and placebo granulation was prepared. Next, chief remedy granulation and placebo granulation were mixed and the tablet with one lock of 100.5mg which tablets the magnesium stearate of cross povidone 5% and a minute amount after powder addition, and contains 10mg of sadium rabeprazole was obtained. Each formula was shown in Table 6.
[0039]
[Table 6]

表6　湿式造粒法による錠剤処方

	処方	実施例4	実施例5	実施例6	実施例7	実施例8	実施例9
主薬顆粒	ラベプラゾールナトリウム(結晶質)	10.0	10.0	10.0	10.0	10.0	10.0
	無水Na2CO3	-	-	-	5.0	5.0	10.0
	マンニトール	82.0	30.0	20.0	25.0	15.0	20.0
	ヒドロキシプロピルセルロース	2.0	1.0	0.7	1.0	0.7	1.0
	(小計)	94.0	41.0	30.7	41.0	30.7	41.0
プラセボ顆粒	マンニトール	-	52.0	62.1	52.0	62.1	52.0
	ヒドロキシプロピルセルロース	-	1.0	1.2	1.0	1.2	1.0
	(小計)	0.0	53.0	63.3	53.0	63.3	53.0
粉添部	クロスポビドン	5.0	5.0	5.0	5.0	5.0	5.0
	ステアリン酸マグネシウム	1.5	1.5	1.5	1.5	1.5	1.5
	(小計)	6.5	6.5	6.5	6.5	6.5	6.5
	総計	100.5	100.5	100.5	100.5	100.5	100.5

単位:mg

[0040] 0, 2.5 or 5% of three levels and **, and others obtained the tablet for the example 10 - the amount of 12 powder-addition cross povidone by the same approach as examples 4-9. The formula was shown in Table 7.
[0041]

[Table 7]

表7　湿式造粒法によるクロスポビドン添加の錠剤処方

	処方	実施例10	実施例11	実施例12
主薬顆粒	ラベプラゾールナトリウム(結晶質)	10.0	10.0	10.0
	無水Na2CO3	5.0	5.0	5.0
	マンニトール	25.0	25.0	25.0
	ヒドロキシプロピルセルロース	1.0	1.0	1.0
	(小計)	41.0	41.0	41.0
プラセボ顆粒	マンニトール	56.9	54.4	52.0
	ヒドロキシプロピルセルロース	1.1	1.1	1.0
	(小計)	58.0	55.5	53.0
粉添部	クロスポビドン	–	2.5	5.0
	ステアリン酸マグネシウム	1.5	1.5	1.5
	(小計)	1.5	4.0	6.5
	総計	100.5	100.5	100.5

単位:mg

[0042] the example of 2 formulas shown in 13 to example 14 table 8 -- following -- sadium rabeprazole 100g -- sodium-carbonates 0-50g, Mannitols 79.3-84.3g, and cross povidone 4.2g and 1.5g of magnesium stearates -- respectively -- adding -- enough -- mixing -- direct -- a making tablet -- carrying out -- sadium rabeprazole 10mg -- the tablet with one lock of 100mg included was obtained.

[0043]

[Table 8]

表8　直接打錠法による錠剤処方

処方	実施例13	実施例14
ラベプラゾールナトリウム(結晶質)	10.0	10.0
無水Na2CO3	–	5.0
マンニトール	84.3	79.3
クロスポビドン	4.2	4.2
ステアリン酸マグネシウム	1.5	1.5
総計	100.0	100.0

単位:mg

[0044] It was easy to add 50g of sodium carbonates, and 2g of magnesium stearates to example 15 sadium-rabeprazole 100g respectively, it mixed, dry type compression granulation was carried out, and chief remedy granulation was prepared. Moreover, churning wet agglomeration was performed adding gradually hydroxypropylcellulose 2.3g which was easy to add mannitol 76.3g and cross povidone 4.2g respectively, mixed,

and was independently dissolved in ethanol, and placebo granulation was prepared. Next, chief remedy granulation and placebo granulation were mixed and the tablet with one lock of 100mg which contains 10mg of sadium rabeprazole as the magnesium stearate of a minute amount is tableted and is shown in Table 9 after powder addition was obtained.
[0045]
[Table 9]

表9　乾式造粒法による錠剤処方

	処方	実施例15
主薬顆粒	ラベプラゾールナトリウム(結晶質)	10.0
	無水Na2CO3	5.0
	ステアリン酸マグネシウム	0.2
	(小計)	15.2
プラセボ顆粒	マンニトール	76.8
	クロスポビドン	4.2
	ヒドロキシプロピルセルロース	2.3
	(小計)	83.3
粉添部	ステアリン酸マグネシウム	1.5
	総計	100.0

単位：mg

[0046] Cross povidone 527g and hydroxypropylcellulose 20g ** from which a mean diameter differs in example 16 - 18 sadium-rabeprazole 100g were mixed, and the tablet with one lock of 65mg which contains 10mg of sadium rabeprazole as 3g magnesium stearate is tableted and is shown in Table 10 after powder addition was obtained. In addition, the used cross povidone is the product of BASF A.G., and the mean particle diameter is the hammer mill grinding article (6 micrometers) of Kollidon CL (51 micrometers), Kollidon CLM (12 micrometers), and Kollidon CLM.
[0047]
[Table 10]

表10 平均粒径の異なるクロスポビドン添加の処方

処方	実施例16	実施例17	実施例18
ラベプラゾールナトリウム	10.0	10.0	10.0
クロスポビドン(コリドンCL)	52.7	–	–
クロスポビドン(コリドンCLM)	–	52.7	–
クロスポビドン(コリドンCLMの粉砕品)	–	–	52.7
ヒドロキシプロピルセルロース	2.0	2.0	2.0
ステアリン酸マグネシウム	0.3	0.3	0.3
(小計)	65.0	65.0	65.0

単位:mg

注)平均粒径

クロスポビドン(コリドンCL) : 51μm

クロスポビドン(コリドンCLM) : 12μm

クロスポビドン(コリドンCLMの粉砕品) : 6μm

The middle coat of the water-insoluble nature which contains ethyl cellulose, cross povidone, and magnesium stearate for the nucleus part containing 19 to example 20 sadium rabeprazole after granulation by ethanol was coated. Next, the enteric sex skin film covering tablet and the tablet which covered both enteric sex skin film and moisture-proof sex skin film were obtained by giving the further coat. In addition, the formula was shown in Table 11.

[0048]

[Table 11]

表11 腸溶性製剤及び防湿性皮膜を施した製剤の処方

	処方	実施例19	実施例20
核部分	ラベプラゾールナトリウム	10.0	10.0
	マンニトール	36.2	36.2
	クロスポビドン	15.6	15.6
	水酸化ナトリウム	0.1	0.1
	無水炭酸ナトリウム	5.0	5.0
	ヒドロキシプロピルセルロース	2.0	2.0
	ステアリン酸マグネシウム	1.1	1.1
	(小計)	70.0	70.0
中間皮膜	エチルセルロース	0.5	0.5
	クロスポビドン	1.0	1.0
	ステアリン酸マグネシウム	0.1	0.1
	(小計)	1.6	1.6
腸溶性皮膜	ヒドロキシピロピルメチル		
	セルロースフタレート	8.0	8.0
	モノグリセライド	0.8	0.8
	タルク	0.75	0.75
	酸化チタン	0.4	0.4
	黄色酸化鉄	0.05	0.05
	(小計)	10.0	10.0
防湿性皮膜	ヒドロキシピロピルメチル		
	セルロース	–	3.0
	マクロゴール	–	0.6
	タルク	–	1.4
	(小計)		5.0
総計		81.6	86.6

単位:mg

[0049] The tablet which gave the water-soluble middle coat which changes from hydroxypropylcellulose to a nucleus part as a placebo lock which does not contain an example 21 - 23 benzimidazole system compound was prepared. The moisture-proof sex skin film covering pharmaceutical preparation which carried out the spray of the solution which changes from white soft sugar or HA (Sankyo) to the enteric sex skin film covering tablet and enteric sex skin film covering tablet which coated this tablet with the enteric sex skin film was prepared. In addition, the formula was shown in Table 12.

[0050]

[Table 12]

表12 プラセボ処方

	処方	実施例21	実施例22	実施例23
核部分	マンニトール	31.8	31.8	31.8
	クロスポビドン(コリドンCLM)	27.7	27.7	27.7
	ヒドロキシプロピルセルロース	5.0	5.0	5.0
	ステアリン酸マグネシウム	0.5	0.5	0.5
	(小計)	65.0	65.0	65.0
中間皮膜	ヒドロキシプロピルセルロース	3.0	3.0	3.0
腸溶性皮膜	ヒドロキシピロピルメチル			
	セルロースフタレート	8.0	8.0	8.0
	モノグリセライド	0.8	0.8	0.8
	タルク	0.75	0.75	0.75
	酸化チタン	0.4	0.4	0.4
	黄色酸化鉄	0.05	0.05	0.05
	(小計)	10.0	10.0	10.0
防湿性皮膜	白糖	–	10.0	–
	HA(三共)*	–	–	10.0
総計		78.0	88.0	88.0

単位:mg

注:HA(三共)*
ポリビニルアセタールジエチルアミノアセテート、
ヒドロキシピロピルメチルセルロース、
マクロゴール、タルクの混合物

[0051] The tablet containing the cross povidone, sodium hydroxide, and sodium carbonate from which 24 to example 26 sadium rabeprazole and the amount of peroxides differ was obtained by wet granulation according to the formula of Table 13.

[0052]

[Table 13]

表13 過酸化物含量の異なるクロスポビドンを含有する処方

処方	実施例24	実施例25	実施例26
ラベプラゾールナトリウム	10.0	10.0	10.0
マンニトール	36.9	36.9	36.9
クロスポビドン(INF－10) ＊1	14.0	－	－
クロスポビドン(INF－10) ＊2	－	14.0	－
クロスポビドン(コリドンCLM) ＊3	－	－	14.0
クロスポビドン(コリドンCL)	14.0	14.0	14.0
水酸化ナトリウム	0.5	0.5	0.5
無水炭酸ナトリウム	2.5	2.5	2.5
ヒドロキシプロピルセルロース	2.0	2.0	2.0
ステアリン酸マグネシウム	1.1	1.1	1.1
(計)	70.0	70.0	70.0

単位:mg

注)
クロスポビドン(INF－10) ＊1 :(過酸化物含量:18ppm)
クロスポビドン(INF－10) ＊2 :(過酸化物含量:190ppm)
クロスポビドン(コリドンCLM) ＊3:(過酸化物含量:310ppm)

[0053] Adding fines cross povidone 43.5g and hydroxypropylcellulose 6g to example 27 sadium-rabeprazole 30g, and fully mixing, the ethanol solution (solution made to dissolve 1.5g of sodium hydroxides in ethanol) of a sodium hydroxide is added gradually, and is corned, and a particle size regulation is carried out with a small speed mill after desiccation. Into particle size regulation granulation, 3% of cross povidone and 1.6% of magnesium stearate were added, and it mixed into it, and tableted into it, and the tablet with one lock [containing 10mg of sadium rabeprazole] of 70mg was obtained.

[0054] The water ethanol liquid which uses fluidized bed granulator for the tablet obtained in the example 28 example 27, and contains the magnesium stearate of hydroxypropylcellulose and a minute amount was coated, and the tablet with which regular placing of the 2mg of the middle coats was carried out was obtained. Next, the spray of the water ethanol liquid containing hydroxypropylcellulose phthalate, monoglyceride, talc, and titanium oxide was carried out to the middle coat covering tablet using fluidized bed granulator, and the enteric coated tablets with which 10mg of enteric sex skin film was covered was obtained.

[0055] The spray of the purified water which uses fluidized bed granulator for the enteric coated tablets obtained in the example 29 example 28, and contains the hydroxypropyl methylcellulose, macrogol 6000, and talc was carried out, and the tablet with which 5mg of moisture-proof sex skin film was covered was obtained.

PRIOR ART

[Description of the Prior Art] A benzimidazole system compound or its alkali-metal salt has the so-called strong inhibitory action of a proton pump, and is widely used as therapy agents, such as a gastric ulcer and a duodenal ulcer, by controlling gastric-acid secretion. On the other hand, various devices are made [in / since it is chemical very unstable / in a

benzimidazole system compound / pharmaceutical-preparation-izing]. For example, the process of the stable physic constituent characterized by to blend the basic mineral salt of magnesium and/or calcium at JP,62-277322,A at a benzimidazole system compound is indicated, and the oral physic pharmaceutical preparation which blends an alkali compound with the nucleus part which contains a benzimidazole system compound in JP,62-258320,A, covers with a film formation compound water-soluble with the excipient of the tablet quickly disassembled with water solubility thru/or water or a polymer etc., and is further covered with the enteric sex skin film is indicated.

EFFECT OF THE INVENTION

[Effect of the Invention] According to this invention, stabilization of a very unstable benzimidazole system compound is possible. The example of effectiveness is shown below.

450mg of additives shown in example sadium rabeprazole of experiment 50mg and the following table was mixed with the mortar. This was put into the transparent carboy, it saved for one week at a cool place, 60 degrees C, and 75% of 40-degree-C relative humidity, and the content was measured with high performance chromatography. The survival rate under the monograph affair when making the content of a cool place preservation article into 100% was shown in Tables 1-3. Moreover, viewing estimated the tinctorial change of a color. In Table 1, the crystalline substance was used for sadium rabeprazole in an amorphous substance, Table 2, and Table 3. In addition, what blended the hydroxypropylcellulose (front Naka L-HPC and display) used as disintegrator besides an amorphous sadium rabeprazole independent as contrast in Table 1 is used. The sample which blended the polyvinyl pyrrolidone (front Naka PVP and display) used as a binder in Table 3 was used using what blended the aluminum hydroxide (front Naka (OH) aluminum 3 and display) which is the alkaline mineral salt further used as antacid in Table 2.

[0020]

[Table 1]

表1　ラベプラゾールナトリウム(非晶質)の接触試験

		60℃	40℃-75%RH
対照	ラベプラゾールナトリウム(非晶質)	99.1	93.9
	ラベプラゾールナトリウム+L-HPC	80.4	73.3
本願	ラベプラゾールナトリウム+クロスポビドン	98.1	90.4

単位:%

[Table 2]

表2　ラベプラゾールナトリウム(結晶質)の接触試験

		60℃	40℃-75%RH
対照	ラベプラゾールナトリウム(結晶質)	99.8	91.8
	ラベプラゾールナトリウム+L-HPC	62.2	75.0
	ラベプラゾールナトリウム+Al(OH)3	36.9	26.2
本願	ラベプラゾールナトリウム+クロスポビドン	93.3	89.5
	ラベプラゾールナトリウム+Na2CO3	99.1	90.3
	ラベプラゾールナトリウム+Arg・Asp	97.5	90.7

単位:%

[Table 3]

表3　ラベプラゾールナトリウム(結晶質)の接触試験

		60℃	40℃-75%RH
対照	ラベプラゾールナトリウム(結晶質)	97.3	86.9
	ラベプラゾールナトリウム+PVP	89.5	67.7
本願	ラベプラゾールナトリウム+		
	ヒドロキシプロピルセルロース	92.0	86.9
	ラベプラゾールナトリウム+Na2CO3	93.0	82.8
	ラベプラゾールナトリウム+NaOH	91.6	98.8
	ラベプラゾールナトリウム+KOH	92.6	96.8
	ラベプラゾールナトリウム+ オイドラギットE	102.4	86.0
	ラベプラゾールナトリウム+K2CO3	104.5	81.3

単位：%

the tinctorial change of the combination sample concerning the invention in this application is all small as compared with contrast -- it cut. Furthermore, the sodium carbonate which starts the invention in this application from the result of the content stability of Tables 1-3 (front Naka Na2CO3 and display), Potassium carbonate (front Naka K2CO3 and display), a sodium hydroxide (front Naka NaOH and display), A potassium hydroxide (front Naka KOH and display), Aminoalkylmetaacrylatecopolymer E (front Naka OIDORAGITTO E (trademark) and display) It is clear cross povidone's [an arginine aspartic-acid salt (front Naka Arg-Asp and display), hydroxypropylcellulose, and] to stabilize a benzimidazole system compound.

[0023] After saving the tablet with which the sodium-carbonate additions obtained in the examples 4-9 shown in the effectiveness following of the sodium carbonate in a tablet differ for one week at 75% of 40-degree-C relative humidity, the sadium rabeprazole content in the tablet measured with the high speed liquid chromatography was shown in Table 4.

[0024]

[Table 4]

表4　湿式造粒法による錠剤処方の安定性評価

処方	実施例4	実施例5	実施例6	実施例7	実施例8	実施例9
(1週間)						
冷所	99.4	99.0	98.7	99.4	99.5	98.9
40℃-75%RH	83.8	86.7	85.1	92.5	92.8	95.5
(1ヶ月)						
冷所	99.7	99.7	99.7	99.7	99.7	99.6
25℃-75%RH	97.8	98.5	98.3	99.2	99.3	99.3

単位：%

[0025] Since the sadium rabeprazole content stability in a tablet improves depending on the addition of a sodium carbonate, the addition effectiveness of the sodium carbonate in this invention is clear.

[0026] After saving the tablet with which the additions of the cross povidone powder obtained in the examples 10-12 shown in the effectiveness following of the cross povidone in a tablet differ for one week at 75% of 40-degree-C relative humidity, the

sadium rabeprazole content in the tablet measured with the high speed liquid chromatography was shown in Table 5. Moreover, there were so few tinctorial changes of a tablet that there were many additions of cross povidone powder about change of the color of a tablet.

[0027]

[Table 5]

表5　混式造粒法によるクロスポビドン添加錠剤の安定性

処方	実施例10	実施例11	実施例12
(1週間)			
冷所	99.7	99.7	99.7
40°C-75%RH	97.8	98.5	98.3
(1ヶ月)			
冷所	99.4	99.0	98.7
40°C-75%RH	83.8	85.7	85.1

単位：%

It is distinct that the stability of a benzimidazole system compound will improve if cross povidone is added.

[0028] After saving respectively the thickness of the tablet which added the cross povidone from which the mean diameter obtained in the examples 16-18 shown in the effectiveness following of the pulverization cross povidone in a tablet differs for one month at a cool place and 75% of 25-degree-C relative humidity, it was measured, and the expansion coefficient to the cool place preservation tablet of 75% preservation tablet of 25-degree-C relative humidity was evaluated. Consequently, the expansion coefficients of the tablet containing cross povidone (51 micrometers of mean diameters, 12 micrometers, and 6 micrometers) were 1.61, 1.48, and 1.43 respectively. In order that the degree of swelling of a tablet may decrease so that it is made fines with small mean particle diameter, cross povidone's check crack and deformation resulting from expansion of a tablet decrease. Therefore, the pulverization of contribute [to the improvement in stability of the configuration of a tablet] of cross povidone is clear.

[0029] after saving the enteric sex skin film covering tablet obtained in the examples 19-20 shown in the effectiveness following of the moisture-proof sex skin film given to the pharmaceutical preparation which covered the enteric sex skin film, and the tablet which covered both enteric sex skin film and moisture-proof sex skin film for one week at 75% of 25-degree-C relative humidity -- the relative of the sadium rabeprazole in a tablet -- the amount of substance was measured with high performance chromatography. consequently, the relative of an enteric sex skin film covering tablet and the tablet which covered both enteric sex skin film and moisture-proof sex skin film -- the amounts of substance were each, 2.88%, and 2.23%. It is clear pharmaceutical preparation's which covered both enteric sex skin film and moisture-proof sex skin film to have an EQC or the stability beyond it as compared with an enteric sex skin film covering tablet.

[0030] After saving respectively the thickness of the placebo tablet obtained in the examples 21-23 shown below for one week at a cool place and 75% of 40-degree-C relative humidity, it was measured, and the expansion coefficient to the cool place preservation tablet of 75% preservation tablet of 40-degree-C relative humidity was

evaluated. Consequently, the expansion coefficients of the tablet which covered the moisture-proof sex skin film which changes from white soft sugar to an enteric sex skin film covering tablet and an enteric sex skin film covering tablet, and the tablet which covered the moisture-proof sex skin film which changes from HA (Sankyo) (mixture of polyvinyl-acetal diethylamino acetate, hydroxy PIROPIRU methyl cellulose, macro gall, and talc) to an enteric sex skin film covering tablet were 1.15, 1.03, and 1.12 respectively. As for the pharmaceutical preparation which covered both enteric sex skin film and moisture-proof sex skin film, it is distinct that the stability of the configuration of a tablet improves as compared with an enteric sex skin film covering tablet since the degree of swelling of the tablet at the time of preservation is small.

[0031] the tablet which added the cross povidone which was obtained in the examples 24-26 shown in the effectiveness following of the anti-oxidant added into the nucleus part containing a benzimidazole system compound, and from which the amount of content peroxides differs -- using -- a high speed liquid chromatography -- the relative of the rabeprazole in a tablet -- the amount of substance was measured. consequently, the early stages of the tablet which added the cross povidone whose peroxide contents are 18 ppm, 190 ppm, and 310 ppm -- a relative -- decomposition of sadium rabeprazole promotes it, so that the amount of substance has many amounts of peroxides which are 0.65% of each, 0.88%, and 1.13%, and are contained in cross povidone -- having -- a relative -- the increment in the amount of substance was accepted.

[0032] Moreover, after the amount of content peroxides could weigh precisely cross povidone 1g which is 201 ppm, could add the sodium sulfite (addition: un-adding, 0.02%, 0.05%, and 0.10% of four levels) and was mixed, the amount of peroxides in mixture was measured according to the method of examining a Japanese pharmacopoeia publication. Consequently, the amounts of peroxides in the constituent whose additions of a sodium sulfite are un-adding, 0.02%, 0.05%, and 0.10% were 201 ppm, 184 ppm, 108 ppm, and 0 ppm respectively, and reduction of the amount of peroxides was accepted, so that the sodium-sulfite addition increased.

[0033] From the above thing, it is distinct by adding an anti-oxidant into the nucleus parts of a benzimidazole system compound and the tablet containing cross povidone that the stability of the benzimidazole system compound in pharmaceutical preparation improves.

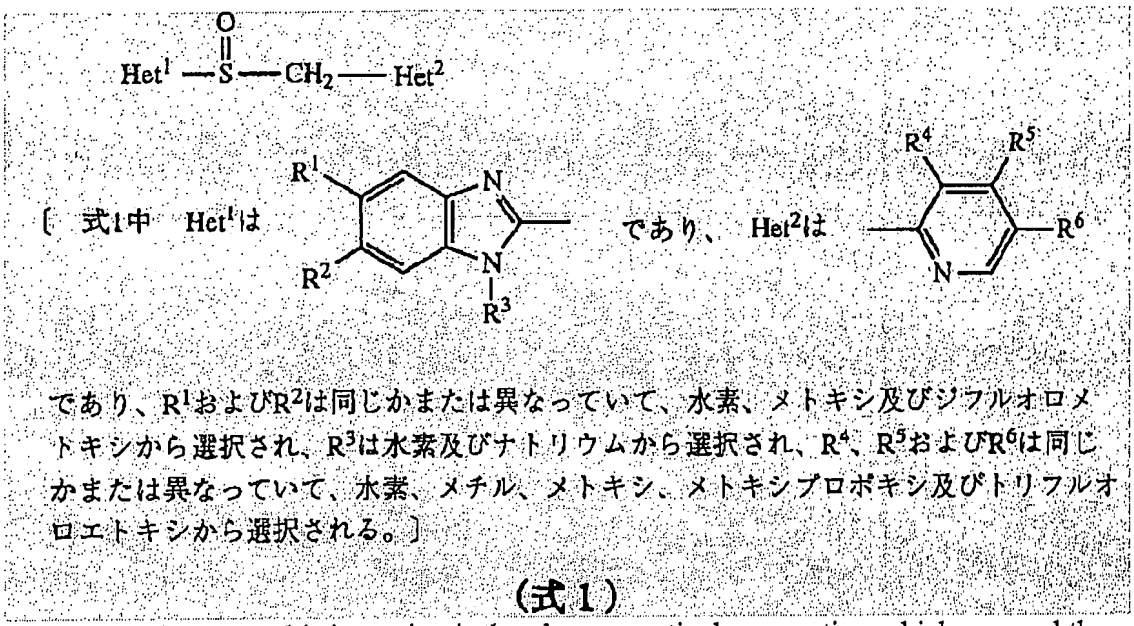
TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] However, also by the above-mentioned technique, the stability in pharmaceutical preparation is not enough and the further improvement is called for. Namely, this invention aims at much more stabilization of the solid preparations for oral administration containing a benzimidazole system compound.

MEANS

[Means for Solving the Problem] This invention is a constituent which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown with the structure expression (formula 1) shown below, or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt,

hydroxypropylcellulose, and cross povidone.
[Formula 2]



(式1)

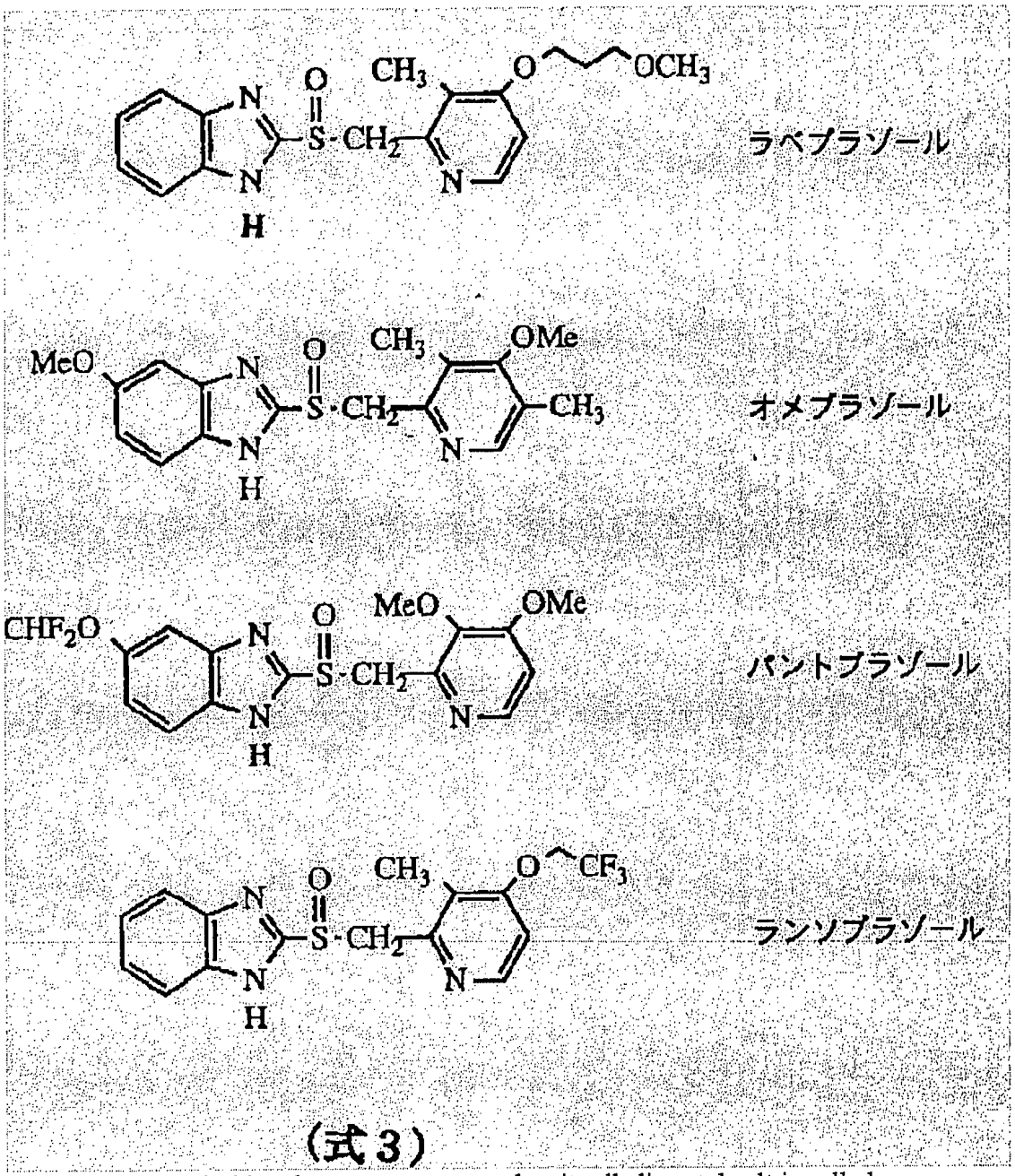
[0005] Furthermore, this invention is the pharmaceutical preparation which covered the enteric sex skin film in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1, or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone. Moreover, this invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1, or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, and covered the enteric sex skin film further. This invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, covered the enteric sex skin film further in the benzimidazole system compound shown by the formula 1, or its alkali-metal salt, and then covered the moisture-proof sex skin film in it again.

[0006] The moisture-proof sex skin film is useful also to the drug with which it does not remain in a benzimidazole system compound, decomposition is promoted under moisture existence, and promotion of decomposition is accepted also at the time of contact to gastric acid. That is, this invention is the pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the enteric sex skin film in gastric acid in the nucleus which comes to blend an unstable drug chemically, and covered the moisture-proof sex skin film further. Moreover, this invention is the pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the middle coat in gastric acid in the nucleus which comes to

blend an unstable drug chemically, covered the enteric sex skin film further, and then covered the moisture-proof sex skin film.

[0007] As a desirable example of the benzimidazole system compound in this invention, or its alkali-metal salt, rabeprazole, omeprazole, punt PURAZORU, lansoprazole or its sodium salt, potassium salt, etc. can be mentioned. The structure expression of each compound is shown in a formula 3.

[Formula 3]



(式3)

Hereafter, a benzimidazole system compound or its alkali-metal salt is called a benzimidazole system compound.

[0008] The benzimidazole system compound in this invention can be manufactured by

the well-known approach. For example, it can manufacture by the approach indicated by JP,52-62275,A, JP,54-141783,A, JP,1-6270,A, etc.
[0009] The sodium carbonate in this invention, potassium carbonate, a sodium hydroxide, a potassium hydroxide, and hydroxypropylcellulose are Japanese pharmacopoeia adoption articles, and can obtain a commercial thing easily. Adoption of the aminoalkylmetaacrylatecopolymer E is carried out to Japanese Pharmaceutical Codex, and it is easily available. Moreover, although cross povidone is matter by which adoption is carried out to excipient specification and is easily available in the commercial item of various grade with which particle size differs, particle size can be adjusted using grinding equipments, such as a hammer mill, if needed. To the benzimidazole system compound 1 weight section, the rate of a compounding ratio with one or more sorts of matter chosen from the benzimidazole system compound in this invention, a sodium carbonate and potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone is 0.01 - 20 weight section in a total amount, and is 0.01 - 10 weight ****** preferably. In this invention, a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone can also be used independently, and two or more sorts can also be used combining these. It is [among these] effective for a benzimidazole system compound to blend a sodium hydroxide, a potassium hydroxide, and/or a sodium carbonate, and it is still more effective if 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate are blended with a benzimidazole system compound. In the combination of this matter, although the rate of a compounding ratio is 0.01 - 20 weight section to the benzimidazole system compound 1 weight section, cross povidone is [0.5 - 5 weight section, a sodium hydroxide, a potassium hydroxide, and/or a sodium carbonate] 0.01 - 2 weight sections desirably.
[0010] a benzimidazole system compound -- warming -- especially at the time of the decomposition under - humidification preservation conditions, the tinctorial change of a color is accepted greatly. The constituent and/or pharmaceutical preparation which blended the above-mentioned various additives in this invention have the very remarkable effectiveness of controlling not only the improvement in content stability but a tinctorial change.
[0011] In order to manufacture pharmaceutical preparation using the constituent which comes to blend one or more sorts of matter chosen from the benzimidazole system compound concerning this invention, a sodium carbonate and potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, excipients usually used, such as a lactose and a mannitol, can be used. It is desirable to use cross povidone as hydroxypropylcellulose and disintegrator as a binder. Moreover, when the cross povidone generally used as disintegrator pulverizes, it is known that the collapse force as original disintegrator and the swelling force can be decreased. The addition which uses it as a stabilizing agent of a benzimidazole system compound in this invention, and exceeds the addition (usually 10% or less) as usual disintegrator is possible for the small cross povidone of the pulverizing-ized particle size. The pulverizing-ized mean particle diameter of cross povidone has several micrometers - 50

micrometers and 4 micrometers - still more desirable 50 micrometers. Therefore, as for cross povidone, in the constituent or pharmaceutical preparation concerning this invention, it is desirable that mean particle diameter uses several micrometers - 50 micrometers and desirable fines cross povidone with a small particle size of 4 micrometers - 50 micrometers. Of course, fines cross povidone and the usual cross povidone may be used together. Moreover, in cross povidone, although it changes with a manufacture manufacturer or lots, the peroxide of ultralow volume is contained as an impurity in many cases. Since a benzimidazole system compound has the property which is easy to oxidize, it may make an anti-oxidant contain at the time of combination to cross povidone. An anti-oxidant is not necessarily limited to these, although a sodium sulfite, a sodium pyrosulfite, vitamin E, a Rongalite, the thioglycerol, a sodium thiosulfate, an ascorbic-acid salt, acetylcysteine, etc. are mentioned.

[0012] Moreover, this invention is the pharmaceutical preparation which covered the enteric sex skin film in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1 from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone. In this invention, a nucleus means a tablet, a granule, etc. Moreover, as for this invention, the pharmaceutical preparation which covered the enteric sex skin film also contains one or more sorts of matter chosen from a benzimidazole system compound, a sodium carbonate and potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone in regular placing or the nucleus which it comes to coat by using as seed granulation the spherical granulation which consists of purified sucrose, white soft sugar and starch mixture, or crystalline cellulose. The benzimidazole system compound is very unstable in an acid condition, and when a benzimidazole system compound is taken, if it contacts gastric acid in the stomach, it will decompose immediately and it will lose the bioactive. Therefore, in order to prevent the decomposition in the stomach, it is necessary to carry out to the pharmaceutical preparation which does not dissolve within the stomach, i.e., the pharmaceutical preparation which covered the enteric matter in the nucleus containing a benzimidazole system compound.

[0013] Furthermore, this invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend one or more sorts of matter chosen as the benzimidazole system compound shown by the formula 1 from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, and covered the enteric sex skin film further. Since the enteric sex skin film is generally the acid, direct contact to a benzimidazole system compound is not desirable. Then, an inactive middle coat can be given in the middle of the nucleus containing a benzimidazole system compound, and the enteric sex skin film. Inactive is matter which does not have a bad influence on the stability of a benzimidazole system compound here. Any of a water soluble polymer, dissolved water in fuel or the water-dispersion matter, and the water-insoluble nature matter are sufficient as an inactive middle coat, and, specifically, it can mention hydroxypropylcellulose, the hydroxypropyl methylcellulose,

Aminoalkylmetaacrylatecopolymer E, a lactose, a mannitol, starch, crystalline cellulose, ethyl cellulose, vinyl acetate, etc. In addition, when giving a middle coat by the water-insoluble nature matter as indicated by JP,1-290628,A, the particle of water-insoluble nature may be mixed in a coat.

[0014] This invention may cover the moisture-proof sex skin film again to the pharmaceutical preparation which covered the above-mentioned enteric sex skin film. The moisture-proof sex skin film is a coat which controls passage of a steam, and, functionally, the coat which captures a steam and controls the inflow of the steam to the interior is mentioned into the coat to which the coat itself controls the permeability of a steam, or a coat. The moisture-proof sex skin film has the function to prevent a crack and deformation of the tablet originating in the swelling at the time of the pulverizing-ized moisture absorption of cross povidone while it defends invasion of the moisture to a benzimidazole system compound and raises stability. The moisture-proof sex skin film is not necessarily limited to these, although the coat which comes to blend one or more sorts of cellulosics, such as a coat which a water-soluble coat or the water-insoluble sex skin film is sufficient as, for example, consists of polyvinyl-acetal diethylamino acetate, HA Sankyo (mixture of polyvinyl-acetal diethylamino acetate, the hydroxypropyl methylcellulose, stearin acid, and a fumaric acid), polyvinyl alcohol, etc., and hydroxypropylcellulose, hydroxypropyl methylcellulose, ethyl cellulose, the glycocalyx coat which uses white soft sugar as a principal component are mentioned.

[0015] The moisture-proof sex skin film is useful also to the pharmaceutical preparation containing the drug which does not remain in a benzimidazole system compound but has the same chemical property. That is, in the pharmaceutical preparation containing the drug with which decomposition is promoted under moisture existence, and promotion of decomposition is accepted also at the time of contact to gastric acid, effectiveness is accepted notably. That is, this invention is the pharmaceutical preparation which decomposition was promoted under moisture existence, and covered the enteric sex skin film in gastric acid in the nucleus which comes to blend an unstable drug chemically, and covered the moisture-proof sex skin film further. Moreover, a middle coat may be covered between the enteric sex skin film and the moisture-proof sex skin film.

[0016] In this invention, when the benzimidazole system compound expressed with a formula 1 is rabeprazole, the especially excellent effectiveness is shown. That is, this invention is a constituent which comes preferably to blend a sodium hydroxide, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt. Moreover, this invention is a constituent which comes preferably to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt. As for cross povidone, it is desirable to use what pulverized mean particle diameter to several micrometers - 50 micrometers as mentioned above. Moreover, an anti-oxidant may be added in order to prevent the effect of the peroxide of the ultralow volume contained in cross povidone as mentioned above. Therefore, an anti-oxidant may be blended into the constituent which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with rabeprazole or its alkali-metal salt.

[0017] This invention is the pharmaceutical preparation which covered the enteric sex skin film preferably again in the nucleus which comes to blend 1 cross povidone, 2

sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt. Furthermore, this invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes preferably to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt, and covered the enteric sex skin film further. This invention is the pharmaceutical preparation which covered the middle coat in the nucleus which comes to blend 1 cross povidone, 2 sodium hydroxides, a potassium hydroxide, and/or a sodium carbonate with the rabeprazole shown by the formula 3, or its alkali-metal salt, covered the enteric sex skin film further, and then covered the moisture-proof sex skin film preferably again.

[0018] The constituent or pharmaceutical preparation concerning this invention can be manufactured by the approach usually used. That is, for example, one or more sorts of matter chosen as a benzimidazole system compound or its alkali-metal salt from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone is blended, an excipient is added, dry type or wet agglomeration is performed, and if needed, disintegrator, such as cross povidone, can be added, and can be tableted and **(ed). Moreover, for example, after preparing the benzimidazole content granulation which blended with high density one or more sorts of matter chosen from a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, Aminoalkylmetaacrylatecopolymer E, an arginine aspartic-acid salt, hydroxypropylcellulose, and cross povidone, and the placebo granulation which does not contain a benzimidazole system compound, both granulation may be mixed in a benzimidazole system compound or its alkali-metal salt, and you may add and tablet disintegrator, such as cross povidone, in it if needed. Of course, it is not necessarily limited to these approaches. The hydroxypropylcellulose dissolved in ethanol is added gradually, and is corned, mixing sadium rabeprazole 100g [which is a benzimidazole system compound], 30g [of sodium carbonates], and mannitol 130g, and mixing further as an example, and screening is carried out by 24 mesh sieves after desiccation. Cross povidone 30g and 2g of calcium stearates can be added to this, it can tablet after mixing, and a tablet with one lock of 135mg can be obtained. Fluid bed equipment can be used for this tablet, the ethanol solution of hydroxypropylcellulose can be sprayed, and the enteric coated tablets which sprayed hydroxypropylmethylcellulose phthalate, or the water / ethanol solution of an enteric methacrylic acid copolymer, and gave the middle coat can be manufactured further.

EXAMPLE

[Example] Although an example is given to below and this invention is further explained to a detail, this invention is not necessarily limited to these.

[0035] The tablet with one lock of 120mg which adds gradually hydroxypropylcellulose 2.5g dissolved in ethanol, corns and carries out after [desiccation] screening, adds and tablets calcium stearate, and contains 10mg of sadium rabeprazole was obtained having added 10g [of sodium carbonates], and mannitol 100g to example 1 sadium-rabeprazole

10g, and mixing.
[0036] The spray of the solution which dissolved hydroxypropylmethylcellulose phthalate 10g in 2:8 mixed solvents of water ethanol was carried out to the tablet obtained in the example 2 example 1 using fluidized bed granulator, and the enteric coated tablets was manufactured.
[0037] After using fluidized bed granulator for the tablet obtained in the example 3 example 1 and carrying out the spray of the ethanol solution of hydroxypropylcellulose to it, it was operated like the example 2 and the enteric coated tablets was obtained.
[0038] Having added respectively sodium carbonates 0-10g and Mannitols 15-90g to example 4 - 9 sadium-rabeprazole 10g, and mixing, the hydroxypropylcellulose 0.7-2g dissolved in ethanol was added gradually, churning wet agglomeration was carried out, and chief remedy granulation was prepared. Moreover, churning wet agglomeration was performed adding independently hydroxypropylcellulose 2g dissolved in ethanol to mannitol 100g gradually, and placebo granulation was prepared. Next, chief remedy granulation and placebo granulation were mixed and the tablet with one lock of 100.5mg which tablets the magnesium stearate of cross povidone 5% and a minute amount after powder addition, and contains 10mg of sadium rabeprazole was obtained. Each formula was shown in Table 6.
[0039]
[Table 6]

表6　湿式造粒法による錠剤処方

	処方	実施例4	実施例5	実施例6	実施例7	実施例8	実施例9
主薬顆粒	ラベプラゾールナトリウム(結晶質)	10.0	10.0	10.0	10.0	10.0	10.0
	無水Na_2CO_3	–	–	–	5.0	5.0	10.0
	マンニトール	82.0	30.0	20.0	25.0	15.0	20.0
	ヒドロキシプロピルセルロース	2.0	1.0	0.7	1.0	0.7	1.0
	(小計)	94.0	41.0	30.7	41.0	30.7	41.0
プラセボ顆粒	マンニトール	–	62.0	62.1	52.0	62.1	52.0
	ヒドロキシプロピルセルロース	–	1.0	1.2	1.0	1.2	1.0
	(小計)	0.0	53.0	63.3	53.0	63.3	53.0
粉添部	クロスポビドン	5.0	5.0	5.0	5.0	5.0	5.0
	ステアリン酸マグネシウム	1.5	1.5	1.5	1.5	1.5	1.5
	(小計)	6.5	6.5	6.5	6.5	6.5	6.5
	総計	100.5	100.5	100.5	100.5	100.5	100.5

単位:mg

[0040] 0, 2.5 or 5% of three levels and **, and others obtained the tablet for the example 10 - the amount of 12 powder-addition cross povidone by the same approach as examples 4-9. The formula was shown in Table 7.
[0041]
[Table 7]

表7　湿式造粒法によるクロスポビドン添加の錠剤処方

	処方	実施例10	実施例11	実施例12
主薬顆粒	ラベプラゾールナトリウム(結晶質)	10.0	10.0	10.0
	無水Na2CO3	5.0	5.0	5.0
	マンニトール	25.0	25.0	25.0
	ヒドロキシプロピルセルロース	1.0	1.0	1.0
	(小計)	41.0	41.0	41.0
プラセボ顆粒	マンニトール	56.9	54.4	52.0
	ヒドロキシプロピルセルロース	1.1	1.1	1.0
	(小計)	58.0	55.5	53.0
粉添部	クロスポビドン	–	2.5	5.0
	ステアリン酸マグネシウム	1.5	1.5	1.5
	(小計)	1.5	4.0	6.5
	総計	100.5	100.5	100.5

単位：mg

[0042] the example of 2 formulas shown in 13 to example 14 table 8 -- following -- sadium rabeprazole 100g -- sodium-carbonates 0-50g, Mannitols 79.3-84.3g, and cross povidone 4.2g and 1.5g of magnesium stearates -- respectively -- adding -- enough -- mixing -- direct -- a making tablet -- carrying out -- sadium rabeprazole 10mg -- the tablet with one lock of 100mg included was obtained.

[0043]

[Table 8]

表8　直接打錠法による錠剤処方

処方	実施例13	実施例14
ラベプラゾールナトリウム(結晶質)	10.0	10.0
無水Na2CO3	–	5.0
マンニトール	84.3	79.3
クロスポビドン	4.2	4.2
ステアリン酸マグネシウム	1.5	1.5
総計	100.0	100.0

単位：mg

[0044] It was easy to add 50g of sodium carbonates, and 2g of magnesium stearates to example 15 sadium-rabeprazole 100g respectively, it mixed, dry type compression granulation was carried out, and chief remedy granulation was prepared. Moreover, churning wet agglomeration was performed adding gradually hydroxypropylcellulose 2.3g which was easy to add mannitol 76.3g and cross povidone 4.2g respectively, mixed, and was independently dissolved in ethanol, and placebo granulation was prepared. Next, chief remedy granulation and placebo granulation were mixed and the tablet with one

lock of 100mg which contains 10mg of sadium rabeprazole as the magnesium stearate of a minute amount is tableted and is shown in Table 9 after powder addition was obtained.
[0045]
[Table 9]

表9　乾式造粒法による錠剤処方

	処方	実施例15
主薬顆粒	ラベプラゾールナトリウム(結晶質)	10.0
	無水Na2CO3	5.0
	ステアリン酸マグネシウム	0.2
	(小計)	15.2
プラセボ顆粒	マンニトール	76.8
	クロスポビドン	4.2
	ヒドロキシプロピルセルロース	2.3
	(小計)	83.3
粉添部	ステアリン酸マグネシウム	1.5
	総計	100.0

単位：mg

[0046] Cross povidone 527g and hydroxypropylcellulose 20g ** from which a mean diameter differs in example 16 - 18 sadium-rabeprazole 100g were mixed, and the tablet with one lock of 65mg which contains 10mg of sadium rabeprazole as 3g magnesium stearate is tableted and is shown in Table 10 after powder addition was obtained. In addition, the used cross povidone is the product of BASF A.G., and the mean particle diameter is the hammer mill grinding article (6 micrometers) of Kollidon CL (51 micrometers), Kollidon CLM (12 micrometers), and Kollidon CLM.
[0047]
[Table 10]

表10 平均粒径の異なるクロスポビドン添加の処方

処方	実施例16	実施例17	実施例18
ラベプラゾールナトリウム	10.0	10.0	10.0
クロスポビドン(コリドンCL)	52.7	–	–
クロスポビドン(コリドンCLM)	–	52.7	–
クロスポビドン(コリドンCLMの粉砕品)	–	–	52.7
ヒドロキシプロピルセルロース	2.0	2.0	2.0
ステアリン酸マグネシウム	0.3	0.3	0.3
(小計)	65.0	65.0	65.0

単位:mg

注)平均粒径
クロスポビドン(コリドンCL) : 51μm
クロスポビドン(コリドンCLM) : 12μm
クロスポビドン(コリドンCLMの粉砕品) : 6μm

The middle coat of the water-insoluble nature which contains ethyl cellulose, cross povidone, and magnesium stearate for the nucleus part containing 19 to example 20 sadium rabeprazole after granulation by ethanol was coated. Next, the enteric sex skin film covering tablet and the tablet which covered both enteric sex skin film and moisture-proof sex skin film were obtained by giving the further coat. In addition, the formula was shown in Table 11.

[0048]

[Table 11]

表11　腸溶性製剤及び防湿性皮膜を施した製剤の処方

	処方	実施例19	実施例20
核部分	ラベプラゾールナトリウム	10.0	10.0
	マンニトール	36.2	36.2
	クロスポビドン	15.6	15.6
	水酸化ナトリウム	0.1	0.1
	無水炭酸ナトリウム	5.0	5.0
	ヒドロキシプロピルセルロース	2.0	2.0
	ステアリン酸マグネシウム	1.1	1.1
	(小計)	70.0	70.0
中間皮膜	エチルセルロース	0.5	0.5
	クロスポビドン	1.0	1.0
	ステアリン酸マグネシウム	0.1	0.1
	(小計)	1.6	1.6
腸溶性皮膜	ヒドロキシピロピルメチル		
	セルロースフタレート	8.0	8.0
	モノグリセライド	0.8	0.8
	タルク	0.75	0.75
	酸化チタン	0.4	0.4
	黄色酸化鉄	0.05	0.05
	(小計)	10.0	10.0
防湿性皮膜	ヒドロキシピロピルメチル		
	セルロース	-	3.0
	マクロゴール	-	0.6
	タルク	-	1.4
	(小計)		5.0
総計		81.6	86.6

単位：mg

[0049] The tablet which gave the water-soluble middle coat which changes from hydroxypropylcellulose to a nucleus part as a placebo lock which does not contain an example 21 - 23 benzimidazole system compound was prepared. The moisture-proof sex skin film covering pharmaceutical preparation which carried out the spray of the solution which changes from white soft sugar or HA (Sankyo) to the enteric sex skin film covering tablet and enteric sex skin film covering tablet which coated this tablet with the enteric sex skin film was prepared. In addition, the formula was shown in Table 12.

[0050]

[Table 12]

表12 プラセボ処方

	処方	実施例21	実施例22	実施例23
核部分	マンニトール	31.8	31.8	31.8
	クロスポビドン(コリドンCLM)	27.7	27.7	27.7
	ヒドロキシプロピルセルロース	5.0	5.0	5.0
	ステアリン酸マグネシウム	0.5	0.5	0.5
	(小計)	65.0	65.0	65.0
中間皮膜	ヒドロキシプロピルセルロース	3.0	3.0	3.0
腸溶性皮膜	ヒドロキシピロピルメチル			
	セルロースフタレート	8.0	8.0	8.0
	モノグリセライド	0.8	0.8	0.8
	タルク	0.75	0.75	0.75
	酸化チタン	0.4	0.4	0.4
	黄色酸化鉄	0.05	0.05	0.05
	(小計)	10.0	10.0	10.0
防湿性皮膜	白糖	−	10.0	−
	HA(三共)*	−	−	10.0
総計		78.0	88.0	88.0

単位:mg

注 HA(三共)*
ポリビニルアセタールジエチルアミノアセテート、
ヒドロキシピロピルメチルセルロース、
マクロゴール、タルクの混合物

[0051] The tablet containing the cross povidone, sodium hydroxide, and sodium carbonate from which 24 to example 26 sadium rabeprazole and the amount of peroxides differ was obtained by wet granulation according to the formula of Table 13.

[0052]

[Table 13]

表13 過酸化物含量の異なるクロスポビドンを含有する処方

処方	実施例24	実施例25	実施例26
ラベプラゾールナトリウム	10.0	10.0	10.0
マンニトール	36.9	36.9	36.9
クロスポビドン(INF－10) ＊1	14.0	－	－
クロスポビドン(INF－10) ＊2	－	14.0	－
クロスポビドン(コリドンCLM) ＊3	－	－	14.0
クロスポビドン(コリドンCL)	14.0	14.0	14.0
水酸化ナトリウム	0.5	0.5	0.5
無水炭酸ナトリウム	2.5	2.5	2.5
ヒドロキシプロピルセルロース	2.0	2.0	2.0
ステアリン酸マグネシウム	1.1	1.1	1.1
(計)	70.0	70.0	70.0

単位:mg

注)
クロスポビドン(INF－10) ＊1 :(過酸化物含量:18ppm)
クロスポビドン(INF－10) ＊2 :(過酸化物含量:190ppm)
クロスポビドン(コリドンCLM) ＊3:(過酸化物含量:310ppm)

[0053] Adding fines cross povidone 43.5g and hydroxypropylcellulose 6g to example 27 sadium-rabeprazole 30g, and fully mixing, the ethanol solution (solution made to dissolve 1.5g of sodium hydroxides in ethanol) of a sodium hydroxide is added gradually, and is corned, and a particle size regulation is carried out with a small speed mill after desiccation. Into particle size regulation granulation, 3% of cross povidone and 1.6% of magnesium stearate were added, and it mixed into it, and tableted into it, and the tablet with one lock [containing 10mg of sadium rabeprazole] of 70mg was obtained.

[0054] The water ethanol liquid which uses fluidized bed granulator for the tablet obtained in the example 28 example 27, and contains the magnesium stearate of hydroxypropylcellulose and a minute amount was coated, and the tablet with which regular placing of the 2mg of the middle coats was carried out was obtained. Next, the spray of the water ethanol liquid containing hydroxypropylcellulose phthalate, monoglyceride, talc, and titanium oxide was carried out to the middle coat covering tablet using fluidized bed granulator, and the enteric coated tablets with which 10mg of enteric sex skin film was covered was obtained.

[0055] The spray of the purified water which uses fluidized bed granulator for the enteric coated tablets obtained in the example 29 example 28, and contains the hydroxypropyl methylcellulose, macrogol 6000, and talc was carried out, and the tablet with which 5mg of moisture-proof sex skin film was covered was obtained.